

Protocol Number: ACE-LY-002

Protocol Title: An Open-label, Phase 1b Study of ACP-196 in Subjects with Relapsed or Refractory de Novo Activated B-cell (ABC) Subtype of Diffuse Large B-Cell Lymphoma

Version: 2.0

Version date: 20 March 2018

*The undersigned have reviewed this plan and find it to be consistent with the requirements of the protocol as it applies to their respective areas*

Prepared by

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## Statistical Analysis Plan

**An Open-label, Phase 1b Study of ACP-196 in Subjects with Relapsed or  
Refractory de Novo Activated B-cell (ABC) Subtype of Diffuse Large B-Cell  
Lymphoma**

**Protocol Number: ACE-LY-002**

**Version:**  
**Date:**  
**Study Statistician:**

**Version 2.0**  
**20 March 2018**



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## **TABLE OF ABBREVIATIONS**

ABC	activated B-cell
AE(s)	adverse event(s)
BID	twice per day
BTK	Bruton's tyrosine kinase
CI	confidence interval
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
IPD	important protocol deviation
IPI	International prognostic index
LHD	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NK	natural killer
NCI	National Cancer Institute
ORR	overall response rate
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PT	preferred term
R-IPI	revised international prognostic index
R/R	relapsed or refractory
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD	stable disease
SD	standard deviation
SOC	system organ class
TEAE(s)	treatment-emergent adverse events
WHO	World Health Organization

## **1. INTRODUCTION**

The purpose of this statistical analysis plan (SAP) is to provide details of efficacy and safety analyses that have been outlined within protocol amendment 3 for study ACE-LY-002, entitled “An Open-label, Phase 1b Study of ACP-196 in Subjects with Relapsed or Refractory de Novo Activated B-cell (ABC) Subtype of Diffuse Large B-Cell Lymphoma” dated January 13, 2016. The original SAP based on same protocol was for interim safety clinical study report (CSR) to support the new drug application (NDA). This SAP is updated to include efficacy analysis. Any changes to the methods described in the final SAP will be documented in the clinical study report (CSR).

Separate reports will be generated for pharmacokinetics (PK) and pharmacodynamics (PD) data.

Hereafter, acalabrutinib (a generic name for ACP-196) will be used in place of ACP-196 in this document.

The analysis will be executed by the biometrics department of Acerta Pharma unless otherwise specified.

## **2. OBJECTIVES**

### **2.1 Primary Objective**

- To characterize the safety profile of acalabrutinib in subjects with relapsed or refractory (R/R) ABC subtype of diffuse large B-cell lymphoma (DLBCL).

### **2.2 Secondary Objectives**

- To characterize the PK profile of acalabrutinib.
- To evaluate the PD effects of acalabrutinib.
- To evaluate the activity of acalabrutinib as measured by response rate, duration of response (DOR), time-to-next treatment, and progression-free survival (PFS).

## **3. STUDY OVERVIEW**

### **3.1 Study Design**

This study is a multicenter and open-label study. Twenty subjects, 10 relapsed and 10 refractory, will be enrolled and will take 100 mg of acalabrutinib twice per day (BID).

Relapsed subjects will be defined as subjects who have had a partial response (PR) or

better (Cheson 2014 or Cheson 2007 criteria) from the previous anticancer therapy and have now progressed. Refractory subjects will be defined as subjects whose best response to the previous anticancer therapy was stable disease (SD) or who did not respond to therapy.

Treatment with acalabrutinib may be continued until disease progression or an unacceptable drug-related toxicity occurs. Tumor assessments will be performed at 8- to 12-week intervals during the trial. All subjects who discontinue study drug will have a safety follow-up visit 30 ( $\pm 7$ ) days after the last dose of study drug unless they have started another cancer therapy within that timeframe.

All subjects will have hematology, chemistry, and urinalysis safety panels done at screening. Once dosing commences (Day 1), all subjects will be evaluated for safety, including serum chemistry and hematology, once weekly for the first 4 weeks, every 2 weeks in Cycle 2 and monthly thereafter. PK and PD testing will be done in Cycle 1 and Cycle 2. Subjects showing clinical benefit and who are tolerating acalabrutinib may remain on study through the end of Cycle 12. The end of trial is defined as the point when the last subject enrolled completes the end of Cycle 12 or withdraws for any reason and completes the 30-day follow-up visit (if applicable), whichever occurs first.

### **3.2 Sample Size**

The trial design is specified because of its practical simplicity and use of a biomarker, rather than power considerations. The sample size of 20 subjects in a Phase 1b study is considered adequate to evaluate the initial safety, PK/PD, and activity of acalabrutinib in this patient population.

## **4. STUDY ENDPOINTS**

### **4.1 Primary Endpoints**

Primary endpoints are:

- Frequency and severity of AEs/SAEs.
- Frequency of AEs requiring discontinuation, dose delay or dose modification of study drug.

### **4.2 Secondary Endpoints**

Secondary efficacy endpoints are:

- Overall response rate (ORR) per Lugano criteria as assessed by investigator;
- DOR per Lugano criteria as assessed by investigator;
- PFS per Lugano criteria as assessed by investigator;
- Time-to-next treatment per Lugano criteria as assessed by investigator.

Secondary PK/PD endpoints are:

- Plasma PK of acalabrutinib;
- Occupancy of BTK by acalabrutinib in peripheral blood mononuclear cells;
- The effect of acalabrutinib on biologic markers of B-cell function.

#### **4.3 PK and PD Parameters**

Refer to separate reports for PK and PD parameters.

### **5. HYPOTHESES AND MULTIPLICITY**

No formal statistical hypotheses will be tested. The clinical hypotheses are that acalabrutinib monotherapy is safety and effective in subjects with R/R DLBCL.

### **6. ANALYSIS SETS**

#### **6.1 All-treated Population**

All-treated population is defined as all enrolled subjects who receive  $\geq 1$  dose of study drug. All-treated population will be used for evaluating the safety and efficacy unless otherwise specified.

### **7. INTERIM ANALYSIS AND EARLY STOPPING GUIDELINES**

No formal interim analysis will be conducted.

### **8. FINAL ANALYSIS AND CLINICAL STUDY REPORT**

The final analysis of primary and secondary efficacy endpoint will occur at the end of trial. The end of trial is defined as when last patient enrolled completes the end of Cycle 12, or withdraws for any reason and completes the 30-day follow-up visit, whichever occurs first. The CSR will be written based on the final analysis.

### **9. MISSING VALUES**



## **9.1 Missing Safety Data**

Conservative imputation rules will be applied in handling partial or missing dates for AE onset and stop dates, start and end dates of concomitant medication, start date of subsequent anticancer therapy, date of initial diagnosis and death date. If dates are completely missing, no imputation will be made. The details of imputation algorithm for dates are included in Appendix 13.2.

Missing safety data other than partial dates will not be imputed.

## **9.2 Missing Efficacy Data**

The method of handling missing data and censoring data is described in the definition for each of the efficacy endpoints, mentioned at section 13.3, 13.4 and 13.5.

# **10. STATISTICAL METHODS OF ANALYSIS**

## **10.1 General Principles**

Descriptive statistics will be used to summarize disposition, demographics, baseline characteristics, disease characteristics, prior anticancer therapy, concomitant medication, study drug administration, efficacy and safety outcomes. Descriptive summary of discrete data will be present the sample size and incidence as frequency and percentage. Descriptive summaries of continuous data will be present the sample size, group mean, standard deviation, median, and range.

Confidence intervals (CIs), when presented, will generally be constructed at the 95% level. For binomial variables, the exact method for CIs will be employed unless otherwise specified.

Calculation of time to event or duration of event (e.g., DOR) will be based on actual study day of event rather than nominal visit date.

## **10.2 Subject Accountability**

The number of subjects enrolled by site, country will be presented. Subject disposition will be summarized for all enrolled subjects including the following information:

- Subject status on study drug
- Count and reason for study drug discontinuation

- Subject status on the study
- Count and reason for study termination
- Time on study (months)

### **10.3 Important Protocol Deviations**

Important Protocol Deviations (IPDs) categories are defined and managed by the study team during the IPD reviews throughout the study before database lock. These definitions of IPD categories, sub-category codes, and descriptions will be used during the study. The final IPD list is used to produce the summary of IPDs table and the List of IPDs.

### **10.4 Baseline Data**

#### **10.4.1 Demographics**

- Age (year, continuous)
- Age category (<65 vs. ≥65 years; ≤60 vs. >60 years)
- Gender
- Ethnicity
- Race
- Region (United States, United Kingdom)

#### **10.4.2 Baseline Characteristics**

- Eastern Cooperative Oncology Group (ECOG) performance score
- Height (cm, continuous)
- Weight (kg, continuous)

#### **10.4.3 Baseline Disease Characteristics**

- Time from initial diagnosis to the first dose of study drug (months, continuous)
- Baseline B symptoms (weight loss, fever, night sweats) (yes, no)
- Number of prior therapy regimens (1-2 vs. ≥3 regimens; continuous)
- Autologous stem cell transplant (yes)
- Tumor bulk (<5 cm vs. ≥5 cm)

- Bulky disease defined as tumor bulk  $\geq 10$  cm (yes, no)
- Ann Arbor stage for lymphoma (stage I, II, III, IV; stage 1-II vs. III-IV)
- Bone marrow involvement (yes, no)
- Extranodal disease (yes, no)
- Number of extranodal sites (0-1 vs.  $\geq 2$ )
- Serum lactate dehydrogenase (LHD) (normal, above normal)
- Baseline QTcF (mean, SD, median, min, max)
- International Prognostic Index (IPI) (low, low-intermediate, high-intermediate, high)
- Revised IPI (R-IPI) (very good, good, poor)

## **10.5 Treatment and Medications**

### **10.5.1 Prior Anticancer Therapies**

A prior anticancer therapy is defined as a systemic therapy received by subjects, either as a single or combination therapy, for the treatment of DLBCL with a start or end date earlier than the date of first dose of study drug. Therapies given as a consolidation or for maintenance of a response or remission will not be considered as a separate regimen. Preparatory regimen and transplant will not be considered as separate regimens. Prior number of regimens for DLBCL is the total number of lines of therapy that a subject received for DLBCL before he/she entered this study. The number of lines and type of prior therapy for DLBCL will be summarized.

### **10.5.2 Prior and Concomitant Medications**

Data reported on concomitant medications CRF will be used. Medications started or ended prior to the first dose of study drug will be considered as prior treatment. Concomitant medications are defined as all medications used on or after the first dose of study drug, through the treatment phase, and through 30 days following the last dose of study drug. Using this definition, a medication can be classified as both prior and concomitant medication. The start date and end date will be imputed based on the rules provided in Appendix 13.2. Medications with completely missing start and stop dates will be considered as both prior and concomitant medications.

Except for antineoplastic agents or other systemic therapies for DLBCL after enrollment, prior and concomitant medications will be summarized by the World Health Organization (WHO) Drug Dictionary therapeutic class and preferred term.

### **10.5.3 Exposure to Study Drug**

Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be used to summarize:

- Duration of exposure (the interval (months) between first dose date and last dose date);
- Actual cumulative dose administered (the total dose administered during the drug exposure period)
- Average daily dose (the ratio of actual cumulative dose administered and duration of exposure)
- Relative dose intensities (the ratio of actual cumulative dose to the planned cumulative dose through the drug exposure period)

Dose withholding and dose deduction by dose change reasons will be summarized and presented as the number and percentage of subjects with non-missing data per category. Dose withholding is defined as missing doses for  $\geq 7$  consecutive days. Dose reduction is defined as taking lower dose level (100 mg per day) for  $\geq 3$  consecutive days.

## **10.6 Analyses of Safety Endpoints**

### **10.6.1 Treatment-Emergent Adverse Events (TEAEs)**

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs to a system organ class (SOC) and a preferred term (PT). The severity of AEs will be assessed and graded by the investigator by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 or higher. Treatment related AEs are events assessed by investigator as related to study drug.

Treatment-emergent AEs will be summarized by SOC and PT, and by CTCAE toxicity grade. The drug-related AEs, serious adverse events (SAEs) and drug-related SAEs, AEs leading to treatment discontinuation, drug dose delay and dose modification will be summarized by PT and by CTCAE toxicity grade.

Death information is reported in the study exit CRF for all deaths. Incidences of deaths are to be reported, along with the primary cause of death. A summary table and a listing will be provided for death.

#### **10.6.2 Adverse Events of Clinical Interest**

Adverse events of clinical interest (ECI) corresponding search strategy are defined in section 8.5.1 of the SAP for acalabrutinib integrated summary of safety dated 21March2017.

Subject incidence of ECI will be summarized using the CTCAE Version 4.03 or higher.

#### **10.6.3 Laboratory Test Results**

Laboratory data for hematology, serum chemistry, serum immunoglobulin, and T/B/natural killer (NK) cell counts to 30 days after last dose of study drug or up to the safety follow-up visit date, whichever is later, will be summarized. Applicable laboratory test results will be graded according to CTCAE Version 4.03 or higher. Generic normal ranges specified in American Medical Association (AMA) Manual of Style 10th Edition (2017) will be applied whenever reference ranges are not available.

Shift from baseline to worst grade during the treatment will be provided as shift tables for selected parameters. Figures of selected parameter will be plotted overtime as appropriate.

All-treated subjects with at least one post-baseline lab test result will be included in the tables.

#### **10.6.4 Vital Signs**

Vital signs include systolic blood pressure, diastolic blood pressure, pulse rate, body temperature and respiratory rate. Summary statistics (mean, standard deviation, median, minimum and maximum) will be produced for vital signs at baseline, post-baseline values from the last visit, minimum and maximum post-baseline values, and changes of these post-baseline values from baseline.

All-treated subjects with at least one post-baseline lab test result will be included in the tables.

#### **10.6.5 ECOG Performance Score**

Shift of ECOG score from baseline to worst post-baseline score during the treatment will be provided as a shift table.

#### **10.6.6 Electrocardiogram**

ECG data is collected at screening. The investigator assessment of clinical significance categorized as normal, abnormal but not clinically significant, and abnormal clinically significant, will be summarized. The number of subjects with corrected QT interval (QTc) greater than 480 msec will also be provided. A listing of subjects with abnormal and clinically significant baseline ECG results or QTc > 480 msec will be produced.

### **10.7 Analyses of Efficacy Endpoints**

#### **10.7.1 Definitions**

- Overall Response Rate (ORR)

ORR is defined as the proportion of subjects who achieve a complete response (CR) or partial response (PR) per Lugano criteria as assessed by investigator.

- Duration of Response (DOR)

DOR is defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of definitive DLBCL disease progression or death from any cause. Subjects not meeting the criteria and alive by the analysis data cutoff date will be censored and the detail censoring rules for DOR are summarized in Appendix 13.3.

- Progression-Free Survival (PFS)

PFS is defined as the interval from the start of acalabrutinib therapy to the earlier of the first documentation of objective DLBCL disease progression or death from any cause. Subjects not meeting the criteria and alive by the analysis data cutoff date will be censored and the detail censoring rules for primary and sensitivity analyses of PFS are summarized Appendix 13.4.

- Time-to-Next Treatment

Time-to-next treatment is defined as the time from start of acalabrutinib therapy for DLBCL to the start of the next treatment for DLBCL. Data from subjects who have not received subsequent therapy for DLBCL by the analysis data cutoff date will be

censored and the detail of censoring rules for time-to-next treatment are summarized in Appendix 13.5.

#### **10.7.2 Analysis Methods**

Efficacy analyses will be performed on the R/R cohorts and total. The analysis of ORR, PFS, time-to-next treatment will be conducted on the all-treated population. The analysis of DOR will be conducted on the subset of the all-treated population who achieve CR or PR as the best overall response.

ORR and the corresponding 95% two-sided CI will be calculated using exact binomial distribution. Descriptive statistics will be provided for best overall response. The order of overall response category is: CR>PR>SD>PD. The number and proportion of subjects within each category of overall response as well as the associated 95% CIs will be presented.

The analysis of DOR, PFS, and time-to-next-treatment will be estimated using the Kaplan-Meier (KM) method. KM estimates with 95% CIs will be calculated for event time quartiles, and event-free rates will be calculated at selected timepoints. Given the small sample size, listings for DOR, PFS, and time-to-next treatment will be provided in lieu of summary statistics as appropriate, including the reason for censoring.

### **11. CHANGE FROM PROTOCOL-SPECIFIED ANALYSES**

There is no major change from protocol-specified analyses for safety.

### **12. LITERATURE CITATIONS / REFERENCES**

Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007; 25:579-586.

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059-3067.

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, US DHHS, NIH, NCI; publish date May 28, 2009 (v4.03: June 14, 2010).

Laurie H. Sehn, Brian Berry, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than standard IPI for patients with diffuse large B-cell lymphoma. Blood, 1 March 2007;109:1857-1861.

The American Medical Association (AMA) Manual of Style, SI Conversion Calculator,

<http://www.amamanualofstyle.com/page/si-conversion-calculator>

Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med 2013 Aug 8;369(6):507-516.



### 13. APPENDIX

#### 13.1 Definitions

##### 13.1.1 Study Day

The study day will be calculated refer to the date of first dose of study drug. Study day 1 is defined as the date of first dose of acalabrutinib. For assessments that occur on or after first dose date, study day is defined as (date of assessment – date of first dose + 1). For assessments that occur prior to first dose date, study day is defined as (date of assessment – date of first dose).

##### 13.1.2 Baseline Value and Post-baseline Value

Unless otherwise specified, the baseline value is defined as the last measurement taken on or prior to the first dose of study drug.

$$\text{Change from baseline} = \text{Postbaseline Value} - \text{Baseline Value}$$

$$\text{Percentage change from baseline} = \left( \frac{\text{Change from baseline}}{\text{Baseline}} \right) \times 100\%$$

##### 13.1.3 Duration of Treatment and Time on Study

Duration of treatment will be calculated from the date of the first dose of study drug to the date of the last dose of study drug:

$$\text{Duration of treatment} = (\text{last study drug date} - \text{frist study drug date}) + 1$$

Time on study will be calculated from the date of the first dose of study drug to the date of study exit or analysis data cut-off date, whichever is the earliest.

$$\text{Time on study} = (\text{study exit date or data cut date} - \text{first study medication date}) + 1$$

##### 13.1.4 Average Daily Dose and Relative Dose Intensity

$$\text{Average daily dose (mg per day)} = \frac{\text{Total cumulative dose taken (mg)}}{\text{Duration of treatment}}$$

and

$$\text{Relative dose intensity} = \left( \frac{\text{Total cumulative dose taken}}{\text{Total expected dose}} \right) \times 100\%$$

Where

Total cumulative dose taken =  
sum of actual daily dose taken through the duration of treatment;

Total expected dose = duration of treatment × protocol assigned daily dose

#### **13.1.5 Age**

Age in years will be calculated at the date of enrollment.

#### **13.1.6 Year and Month**

One year equals to 365.25 days and 1 month equals to 30.4375 days.

#### **13.1.7 Treatment-emergent Adverse Events**

Treatment-emergent AEs are defined as those events with onset date (actual or imputed onset date) on or after the date of first dose of acalabrutinib, through the treatment phase to last dose of acalabrutinib, and within 30 days following the last dose of acalabrutinib.

#### **13.1.8 International Prognostic Index (IPI) and Revised-IPI**

The IPI will be derived based on baseline value of 5 prognostic risk: age greater than 60 years; stage III or IV disease; elevated serum LDH; ECOG performance status of 2, 3, or 4; more than 1 extranodal site. One point is assigned for each of the above risk. The sum of the points allotted correlates with the following risk groups: low risk (0-1 points); low-intermediate risk (2 points); high-intermediate risk (3 points); high risk (4-5 points).

The R-IPI is defined based on IPI as: very good (0 points); good (1, 2 points); poor (3,4,5 points).

#### **13.1.9 Extranodal Disease and Bone Marrow Involvement at Baseline**

The data of extranodal sites of lymphoma is reported on Disease History CRF. Subjects with any sites/extra nodal notations box checked other than 'None', 'Spleen' will be considered as having extranodal disease at baseline.

Data reported on 'Bone Marrow Biopsy and Aspirate' CRF will be used to derive bone marrow involvement. Subjects with bone marrow biopsy and aspirate result box checked 'Not Involved' at baseline based on any method of assessment will be considered to have no bone marrow involved at baseline. Subjects with result box

checked 'involved', 'indeterminant' or 'other' will be considered to have bone marrow involvement as a conservative approach.

#### **13.1.10 Tumor Bulk at Baseline**

Data reported on Lymph Node Assessment CRF will be used to derive tumor bulk. Tumor bulk is defined as the largest diameter of a lymph node by CT scan. Bulky disease is defined as tumor bulk equal to or greater than 10.0 cm.

#### **13.2 Imputation Rules for Partial or Missing Dates**

Imputation of partial dates will be made for AE onset and stop dates, start and end dates of prior and concomitant medication, start date of subsequent anticancer therapy, date of initial diagnosis and death date. If dates are completely missing, no imputation will be made. For any partial date with missing year, no imputation will be made.

The general rule for imputation is:

- If only day is missing, then the 15<sup>th</sup> of the month will be used.
- If only year is present, then June 30<sup>th</sup> will be used.

If such imputation date for initial diagnosis is on or after date of first dose, the date of first dose – 1 will be used. If such imputed date for subsequent anticancer therapies is before date of last dose, the date of last dose + 1 will be used.

If the imputed date is for an AE start date and is in the same year and month as the first dose date but before the first dose date, the first dose date will be used, or if the imputed AE start date is after the AE end date, the AE end date will be used. If the imputed date is for an AE start date and is in the same year and month as but after the last dose date + 30 days, the last dose date + 30 days will be used.

If the imputed date is for an AE end date and is after the death date, the date of death will be used, or if the imputed AE end date is before the AE start date, the AE start date will be used.

If death year and month are available but day is missing:

- If mmyyyy for last contact date = mmyyyy for death date, set death date to the day after the last contact date.
- If mmyyyy for last contact date < mmyyyy for death date, set death date to the first day of the death month.

- If mmyyyy for last contact date > mmyyyy for death date, data error and do not impute.

If both month and day are missing for death date or a death date is totally missing, no imputation is made.

### 13.3 Censoring Rules for Duration of Response

Situation	Outcome	Event Description or Censoring Reason	Last Analysis Date
Documented disease progression before initiation of new anticancer therapy or on/before data cutoff date, whichever occurred first, also no more than 1 missing tumor assessments before documented disease progression	Event	Progressive Disease	Earliest date of documented disease progression
Death before initiation of new anticancer therapy or on/before data cutoff date, whichever occurred first, and no documented disease progression with $\geq 2$ consecutive missing tumor assessment before death, also no more than 1 missing tumor assessments before death	Event	Death	Date of Death
New anticancer therapy Initiated before data cutoff date and before documented disease progression or death	Censored	New anti-cancer therapy	Date of last adequate tumor assessment on or prior to initiation of new anticancer therapy
New anti-cancer therapy before data cutoff date for subjects without documented disease progression or death	Censored	New anti-cancer therapy	Date of last adequate tumor assessment on or prior to initiation of new anticancer therapy
No documented disease progression, initiation of new anticancer therapy or death on/before data cutoff date	Censored	Data cutoff	Date of last adequate tumor assessment on or before data cutoff date
Documented disease progression or death after $\geq 2$ consecutive missing tumor assessments	Censored	Consecutive missing tumor assessments	Date of last tumor assessment prior to the missing assessments that demonstrate lack of disease progression
No post-baseline adequate disease assessments	Censored	No post-baseline adequate disease assessments	Date of first dose of study drug
No baseline disease assessments	Censored	No baseline disease assessment	Date of first dose of study drug

#### 13.4 Censoring Rules for Progression-Free Survival

Situation	Outcome	Event Description or Censoring Reason	Last Analysis Date
Documented disease progression before initiation of new anticancer therapy or on/before data cutoff date, whichever occurred first, also no more than 1 missing tumor assessments before documented disease progression	Event	Progressive Disease	Earliest date of documented disease progression
Death before initiation of new anticancer therapy or on/before data cutoff date, whichever occurred first, and no documented disease progression with $\geq 2$ consecutive missing tumor assessment before death, also no more than 1 missing tumor assessments before death	Event	Death	Date of Death
New anticancer therapy Initiated before data cutoff date and before documented disease progression or death	Censored	New anti-cancer therapy	Date of last adequate tumor assessment on or prior to initiation of new anticancer therapy
New anti-cancer therapy before data cutoff date for subjects without documented disease progression or death	Censored	New anti-cancer therapy	Date of last adequate tumor assessment on or prior to initiation of new anticancer therapy
No documented disease progression, initiation of new anticancer therapy or death on/before data cutoff date	Censored	Data cutoff	Date of last adequate tumor assessment on or before data cutoff date
Documented disease progression or death after $\geq 2$ consecutive missing tumor assessments	Censored	Consecutive missing tumor assessments	Date of last tumor assessment prior to the missing assessments that demonstrate lack of disease progression
No post-baseline adequate disease assessments	Censored	No post-baseline adequate disease assessments	Date of first dose of study drug
No baseline disease assessments	Censored	No baseline disease assessment	Date of first dose of study drug

### 13.5 Censoring Rules for Time-to-Next Treatment

Situation	Outcome	Event Description or Censoring Reason	Last Analysis Date
New anticancer therapy on or before data cutoff date	Event	new anticancer therapy	Initiation of new anticancer therapy
New anticancer therapy after data cutoff date	Censored	new anticancer therapy prior to cutoff date	Data cutoff date
No new anti-cancer therapy	Censored	No next treatment	last time prior to the missing assessments that demonstrate lack of DLBCL progression

Protocol Number: ACE-LY-002

Protocol Title: An Open-label, Phase 1b Study of ACP-196 in Subjects with Relapsed or Refractory de Novo Activated B-cell (ABC) Subtype of Diffuse Large B-Cell Lymphoma

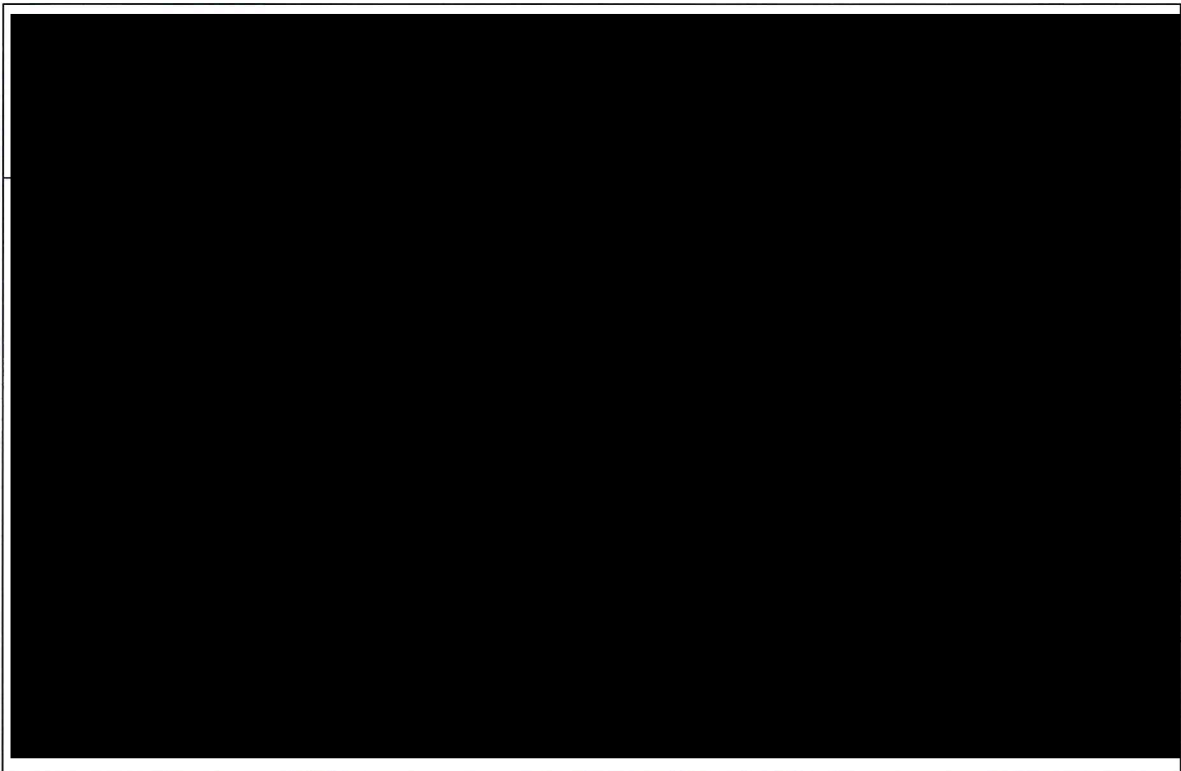
Version: 2.0

Version date: 20 March 2018

*The undersigned have reviewed this plan and find it to be consistent with the requirements of the protocol as it applies to their respective areas*

Prepared by

 Associate Director Biostatistics



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